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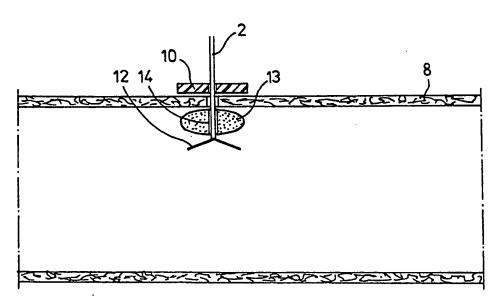
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(54) Title: OCCLUSION ASSEMBLY FOR SEALING OPENINGS IN BLOOD VESSELS AND A METHOD FOR SEAL-ING OPENINGS IN BLOOD VESSELS



(57) Abstract

Occlusion assembly for sealing openings in blood vessels (8) consisting of an occlusion element (13) and fixing element (12) to be fitted through the openings in the blood vessel. The fixing element is firmly connected to a retaining element (2). A locking element (10) engages on the retaining element. This locking element (10) is fitted horizontally against the outside of the blood vessel (8).

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Occlusion assembly for sealing openings in blood vessels and a method for sealing openings in blood vessels.

The invention relates to an occlusion assembly for sealing openings in blood vessels, comprising a spreadable occlusion element which is to be fitted through the opening in the blood vessel and on which a flexible retaining element passing through the wall of the blood vessel engages, a locking element engaging on the retaining element.

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An occlusion assembly of this type is disclosed in US Patent 4,744,364. In this patent it is stated that there is a possibility for sliding a locking element over the retaining element, said locking element then lying against the skin of the user. That is to say, the force necessary to hold the occlusion element against the wall of the blood vessel is led by the retaining element through the outside of the wall of the blood vessel through the skin to the outside of the skin.

With this arrangement, as already indicated, the occlusion. element is located on the inside of the blood vessel. This occlusion element is in general a material which dissolves in time, so that after a few weeks the opening in the wall of the blood vessel is sealed and no further traces of the occlusion element are found. Because the retaining element extends both through the wall of the blood vessel and the adjacent skin, it is very difficult to apply a controlled tension thereto. After all, it is highly conceivable that movement takes place between the blood vessel and the skin, which will result in an uncontrolled high or low tension. In practice, however, it has been found that it is necessary to apply some tension to the retaining element in order to press the occlusion element in a guaranteed manner against the wall of the blood vessel. If this tension is inadequate or is not present, there is a risk that the occlusion element no longer performs its function well, with the possible complication that the occlusion element no longer completely seals the openings, as a result of which very serious consequences can arise. If the tension is too high, there

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is a risk of rupture or of the occlusion element being pulled through the opening in the blood vessel. This means that the occlusion assembly according to US Patent 4.744.364 is either not admissible or is admissible only in situations where it can be guaranteed that there will be no mutual movement between the wall of the blood vessel and the skin during the first few days, that is to say that the patient must remain immobile.

The aim of the present invention is to overcome this disadvantage and to provide an occlusion assembly with which it is possible to apply more tension to the retaining element.

This aim is achieved with an occlusion assembly as described above, in that the occlusion assembly comprises a fixing element, firmly connected to the retaining element, and with which the position of the fixing element on the retaining element is such that, in use, the fixing element lies in the blood vessel against the non-occluding side of the occlusion element. In contrast to the locking element according to the US specification, the locking element according to the present invention is fitted so that it lies horizontally against the wall of the blood vessel. By this means problems relating to mutual shifting of the wall of the blood vessel and the skin, with resultant tension concentrations on the retaining element, are avoided. Because it is now possible to apply greater tension to the retaining element, it can be guaranteed that the occlusion element remains in its place. In practice it has been found that there is then a risk that the occlusion element is pulled through the opening in the wall of the blood vessel. In order to avoid this, the fixing element is fitted.

According to a preferred embodiment of the invention, the fixing element is a curved-plated rod-shaped element and the retaining element is fitted in the centre thereof in such a way that when a force is applied the centre of the rod-shaped element touches the occlusion element first. In this way an even force distribution over the occlusion element is provided.

According to a further advantageous embodiment of the invention, the locking element is to be fitted movably over the retaining element against the outside of the blood vessel.

According to a further advantageous embodiment, at least one

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of the occlusion element or the elements is made from bioabsorbable material. Consequently this part will disappear in time without leaving any trace. According to an advantageous embodiment, the bioabsorbable material comprises collagen or alginate. According to an advantageous embodiment, the occlusion element is in sheet form and essentially circular, heart-shaped or oval. According to a further advantageous embodiment, the occlusion element contains agents which combat stenosis, such as angiotensin II-converting enzyme inhibitor.

The invention also relates to a method for fitting an occlusion assembly in an opening in a blood vessel, comprising the positioning of a sheath through the opening in the blood vessel, guiding an occlusion element and a retaining element, which is coupled therewith, through said sheath into the blood vessel, removing the sheath from the opening in the blood vessel and then placing a locking element on the retaining element. A method of this type is disclosed in US-A-4,744,364. As already indicated above, with this method the locking element is placed horizontally against the skin. It has likewise been stated that this has the disadvantage that it is not possible with this arrangement to guarantee that the tension on the retaining element with which the occlusion element is pressed against the wall of the blood vessel is always sufficient.

The aim of the present method is to provide means of overcoming this disadvantage. This aim is achieved in that the locking element is fitted horizontally against the outside of the blood vessel. By this means effects of mutual movement between the wall of the blood vessel and the skin and any living tissue between the two are avoided. According to an advantageous embodiment of this method, the retaining element is connected to a fixing element, which is inserted in the sheath before the occlusion element.

The invention is illustrated in more detail below with reference to the illustrative embodiments shown in the drawing. In the drawing:

Fig. 1 shows a side view of a first embodiment of the occlusion assembly according to the invention;

Fig. 2 shows a top view of the same embodiment;

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Fig. 3 shows the fitting of the occlusion assembly according to Fig. 1 and 2 in a blood vessel;

Fig. 4 shows the occlusion assembly according to the above embodiment fitted in a blood vessel;

Fig. 5a, b, c show a top view of further embodiments of the occlusion assembly according to the invention;

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Fig. 6 shows a further embodiment of the occlusion assembly according to the invention fitted in a blood vessel;

Fig. 7 shows a side view of a further embodiment of the occlusion assembly according to the invention fitted in a blood vessel.

A side view of a first embodiment of the occlusion assembly according to the invention is shown in Fig. 1. This comprises a flexible sheet 1 as occlusion element and a retaining element 2, which in this case is in the form of a thread, connected to the centre of said occlusion element. A top view of the various features is drawn in Fig. 2.

Fig. 3 shows a blood vessel 8 in which a sheath 6, known for any medical application, has been inserted. After removing the sheath 6, the problem up to now has been that an appreciable opening was formed in the blood vessel which had to be sealed in some way. The means of sealing described in the prior art were found to be unreliable or to impose restrictions in movement on the patient. According to the invention, the assembly shown in Fig. 1 and 2 is inserted through the sheath, as shown. After the occlusion element 1 has been fitted in the blood vessel 8, the unfoldable sheet 1 unfolds in such a way that the surface area thereof is larger than the surface area of the opening to be occluded. Sheath 6 is then moved out of the opening, as a result of which the latter will become somewhat smaller. By pulling on the retaining thread, sheet 1 will come to lie against blood vessel 8 in the manner shown in Fig. 4. By making both the sheet 1 and retaining element 2 of bioabsorbable material, it is ensured that after the opening in the blood vessel has occluded these parts will disappear, for example after a few weeks.

Various other embodiments of the flexible occlusion element or plug 1 are shown in Fig. 5a, b, c. Depending on the possibili-

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ties for insertion through the sheath and the opening made in the blood vessel, these can be used.

A further embodiment of the occlusion assembly according to the invention is shown in Fig. 6. This essentially corresponds to the occlusion assembly described with reference to the above figures, except that a retainer ring 10 is fitted over the fixing thread. This retainer ring 10 or locking element serves for accurate determination of the position of occlusion element 1 and is likewise made of a biologically absorbable material. The ring 10 has an internal diameter such that, on the one hand, it can slide in a supple manner over retaining element 2 but, on the other hand, provides some mutual clamping force on these two parts. In contrast to the prior art, the locking element 10 lies against the outside of the blood vessel 8. Consequently, there is tension in the retaining thread only in the part which must bridge the wall thickness of the blood vessel.

A further embodiment of the invention is shown in Fig. 7. The same reference numerals as in the preceding figures have been used for corresponding parts in this figure. In contrast to the earlier embodiments, the retaining thread 2 is now attached to a fixing element 12 which in this case consists of a rod-shaped curvedplated part. The occlusion element, indicated by 13, is provided with an opening 14 located in the centre, through which the retaining element 2 passes. As a result of the use of the fixing element 12, the tension in the retaining thread 2 can be increased, by which means it is guaranteed that the occlusion element 13 remains in its place. With this arrangement, because of the greater strength of the fixing element, pulling of the occlusion element through the opening in the blood vessel is prevented. The fixing element, as well as the occlusion element and the locking element, can be made of a biocompatible material. The occlusion element can contain angiotensin II-converting enzyme inhibitor, an agent which combats constriction of the blood vessels.

It must be understood that the embodiments described above are merely examples and that the invention is not restricted to these. Thus, the fixing element can comprise all means known in the prior art and is not restricted to the thread shown in the drawing.

Likewise, the unfoldable element to be inserted in the blood vessel can comprise all possible imaginable configurations.

The invention also relates to the use of bioabsorbable material for the production of an occlusion means for sealing puncture holes in blood vessels, as described above.

The outstanding functioning/characteristics of the occlusion means according to the invention are illustrated with reference to results of in vitro and in vivo tests, which are described below.

IN VITRO TESTS

10 Aim:

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Testing occluder with regard to:

- strength of fixing thread/plug connection immediately after insertion and after 1 hour
- 2 pressure resistance of occluder, acute and after 1 hour
- 15 3 "blood tightness", acute and after 1 hour
 - 4 effectiveness of occluder in the case of movements
 - 5 effectiveness of occluder for insertion openings of different diameter

In order to have a criterion for effectiveness, the occlusion frequency is determined with regard to the insertion frequency (ratio of number of effective occlusions to number of times occluder inserted)

- 6 unfolding of plug
- 7 flow pattern of fluid and pressure drop around occluder (turbulence)
 - 8 embolization frequency

Test set-up:

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All tests are carried out with heparinized fresh blood. The following blood parameters are known:

- 30 haemoglobin content (Hb)
 - haematocrit (Ht)
 - platelet content
 - thrombotest (TT)

cephalin time

35 Test set-up for tests 1 to 5 inclusive:

An artery from a test animal (dog, pig) with a diameter of about 7 mm is central in the set-up. This artery is occluded at

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both ends, on one side by means of a clamp and on the other side by means of a valve. Via this valve the lumen of the artery is connected to a bag of blood which is placed in a pressure bag. The pressure in the blood vessel is kept constant at 150 mm Hg. A sheath with a standard internal diameter of 9 French (2.9 mm) is inserted in the artery by means of the customary technique. The maximum diameter of the plug is standard 4.0 mm.

The insertion module is such that this can be inserted through a standard sheath with an internal cross-section of 5 French (1.65 mm).

The following experiments are carried out in this set-up:

- Strength of fixing thread/plug connection immediately after insertion and after 1 hour
- Aim: testing the strength of the fixing thread, the connection between fixing thread and plug and the deformability of the plug under the influence of a force exerted from outside.

 Method: this is tested by hanging a weight of 250 gram on the fixing thread for 15 minutes.
- 2. Pressure resistance of occluder, acute and after 1 hour
 20 Aim: testing the mechanical strength and deformability of the plug under the influence of a force from inside.

 Method: this is tested by increasing the pressure in the blood vessel to 300 mm Hg for 15 minutes.
 - 3. "Blood tightness", acute and after 1 hour
- Aim: testing the amount of blood which passes through the plug and the insertion hole although the plug is mechanically well positioned.
 - Method: this measurement is combined with experiment 2. The amount of blood which has diffused through the plug is measured by collecting this blood on dry gauzes and weighing the gauzes before and after the experiment. The difference in weight in grams is regarded as the amount of diffused blood in ml.
- 4. Effectiveness of occluder in the case of movements

 Aim: testing the stability of the plug when the blood vessel moves.

Method: the vessel is fixed at one end and suspended at the

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other end on an oscillating rod. This rod is moved by an electric motor with a frequency of 1 Hz. A small rod is positioned transversely over the vessel, at about 2 cm from the puncture site, in such a way that said small rod acts as a hinge point for the vessel. The positioning of the vessel is such that the section connected to the rod describes a segment of a circle between 0 and 150°. The puncture site is in the moving part of the vessel. The test time is 30 minutes.

10 5. Effectiveness of occluder for insertion openings of different diameter.

> Aim: testing the effectiveness of the occluder for insertion openings of different diameter.

> the standard plug with a cross-section of 4 mm is inserted after puncture sites have been made with the following internal sheath diameters: 5 French (1.65 mm), 7 French (2.3 mm) and 9 French (2.9 mm). These tests are carried out under standard conditions and are evaluated using the occlusion/insertion ratio (0/I ratio, 100% success = 1, 0% success = 0).

Test set-up for tests 6 to 8 inclusive:

An artery originating from a test animal (dog, pig) with a cross-section of about 7 mm is central in the set-up. The set-up further consists of a roller pump, a heat exchanger, a pressure 25 vessel, a haemofilter and a collection vessel. The blood is pumped from the collection vessel (= atmospheric pressure) by the roller pump into the pressure vessel. The pressure vessel is partially filled with air. An adjustable valve, by means of which the fluid can be kept under pressure, is in the top of the pressure vessel. Any air bubbles entrained in the blood pumped from the collection vessel can be removed in the pressure vessel. From the pressure vessel, the blood flows to the artery via a heat exchanger. Two pressure lines (upstream and downstream of the plug) and a temperature measuring point are fitted in the artery. Downstream of the vessel there is a haemofilter and an adjustable resistance. 35 During the experiment the temperature is kept at 37°C and the pressure upstream of the plug at 150 mm Hg. Flow can be measured

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after passage of the blood through the haemofilter downstream of the vessel downstream of the resistance, before the blood flows back into the collection vessel, by means of a graduated beaker and a chronometer.

- If necessary, the vessel is supported on the outside by a (plastic) tube to simulate the tissue pressure. The position of the insertion opening is left exposed in this case. For evaluation of flow speeds and flow patterns around the plug use can be made of a standard colour Doppler Echo apparatus.
- The following experiments are carried out in this set-up:
 - 6. Unfolding of plug

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Aim: testing to determine whether the plug unfolds as expected.

Method: it is attempted to visualize the plug by means of echography and to determine the shape.

7. Flow pattern of fluid and pressure drop around occluder (turbulence)

Aim: testing to establish that the plug does not cause stenoses.

- Method: after initial measurements of pressure and flow, the plug is inserted. After insertion of the plug these measurements are repeated to determine whether the plug has a stenosing action. The flow pattern around the plug is also visualized with the aid of colour Doppler Echo.
- 25 8. Embolization frequency

Aim: testing to establish that the plug does not act as an embolization source.

Method: after each insertion of the plug, blood is circulated for 2 hours. The haemofilter is then checked and replaced. The pores of the haemofilter are the same size as those of filters used in extracorporal circulation. The number, the size and, where possible, the composition of the emboli are documented.

Tests 6, 7 and 8 can be carried out simultaneously. Tests 6 and 7 are carried out both at the start and just before the end of the experiments.

IN VIVO TESTS

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In the case of in vivo tests the following points are of importance:

- stability of plug
- haemorrhaging rate at the site of the puncture hole
- 5 effect of rapid mobilization on stability of the plug
 - vessel recovery at the puncture site
 - formation of aneurysms at the puncture site
 - frequency of stenosis at the site of the plug
 - absorption of plug and fixing thread with time
- 10 scarring around plug and fixing thread
 - thrombogenicity of plug
 - frequency of embolization of plug material
 - occurrence of infections at the site of the plug
 - toxicity of plug and fixing thread

The test animal is an animal of adequate size (dog, pig). 15 anaesthesia and connection for artificial adequate respiration, a catheter is inserted in the a. carotis for pressure registration. Heparinization is effected Ъу administration of 100 U/kg of body weight. Blood is taken to (Hb). haematocrit (Ht). 20 determine haemoglobin thrombotest (TT) and cephalin time.

A blood vessel of adequate diameter is sought (a. iliaca, aorta). Via a catheter in the a. carotis, an initial angiogram is made of the blood vessel to be punctured. A standard 9 French sheath is inserted, followed by the insertion of the standard plug (diameter 4 mm).

Depending on the size of the selected blood vessel, one or more puncture sites may be made. After inserting the plug, there is a 15 minute period of observation to determine whether the plug remains stable in place and whether there is any "oozing" at the puncture site (semi-quantitative assessment). After the procedure, a check angiography of the punctured vessel segment is made before removing the sheath from the a. carotis. In the event of survival, blood is taken the following day to determine Hb and Ht. A clinical evaluation is also carried out to determine whether there are any emboli. Before termination, a check angiography is made of the punctured vessel segment. After termination, the puncture site is

sought and removed and fixed in formalin (for light microscopy) or glutaraldehyde (for scanning electron microscopy, SEM).

Survival periods in days: 0, 1, 7, 30, 90, 180.

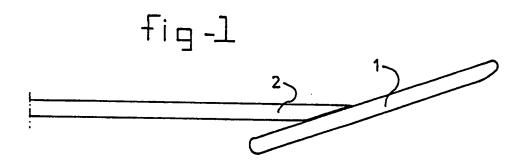
A control group consists of test animals which undergo the same procedure except for the arterial puncture.

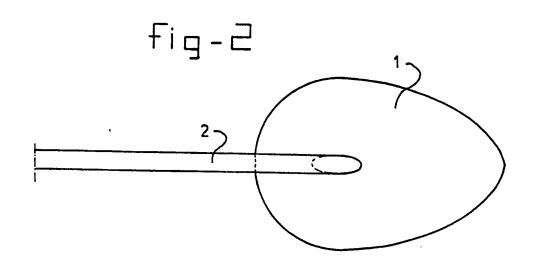
The results of both the in vivo and in vitro tests indicate that the occlusion means according to the invention is outstandingly suitable for the intended application.

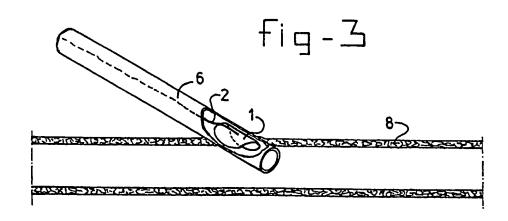
CLAIMS

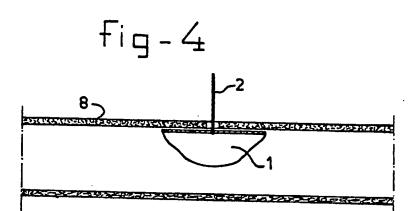
- 1. An occlusion assembly for sealing openings in blood vessels, comprising a spreadable occlusion element which is to be fitted through the opening in the blood vessel and on which a flexible retaining element passing through the wall of the blood vessel engages, a locking element engaging on the retaining element, characterized in that the occlusion assembly comprises a fixing element, firmly connected to the retaining element, and with which the position of the fixing element on the retaining element is such that, in use, the fixing element lies in the blood vessel against the non-occluding side of the occlusion element.
- 2. Occlusion assembly according to Claim 1, wherein the fixing element comprises a curved-plated rod-shaped element and the retaining element is fitted in the centre thereof in such a way that when a force is applied the centre of the rod-shaped element touches the occlusion element first.
- 3. Occlusion assembly according to one of the preceding claims, wherein the locking element is movable along the retaining element in order to lie against the outside of the blood vessel.
- 4. Occlusion assembly according to one of the preceding claims, wherein at least one of the occlusion element or the elements consists of bioabsorbable material.
- 5. Occlusion assembly according to Claim 4, wherein the bioabsorbable material comprises collagen or alginate.
- 6. Occlusion assembly according to one of the preceding claims, wherein the occlusion element is in sheet form and has an essentially circular, heart-shaped or oval shape.
- 7. Occlusion assembly according to one of the preceding claims, wherein the occlusion element contains agents combating stenoses.
- 8. Method for fitting an occlusion assembly in an opening in a blood vessel, comprising the positioning of a sheath through the opening in the blood vessel, guiding an occlusion element and a retaining element, which is coupled therewith, through said sheath into the blood vessel, removing the sheath from the opening in the blood vessel and then placing a locking element on the retaining element, characterized in that the locking element is fitted to lie horizontally against the outside of the blood vessel.

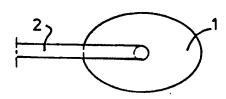
9. Method according to Claim 8, wherein the retaining element is connected to a fixing element, which is inserted in the sheath before the occlusion element.

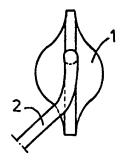


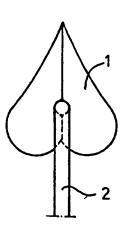


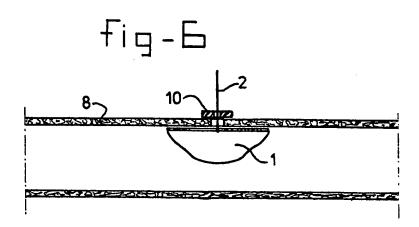


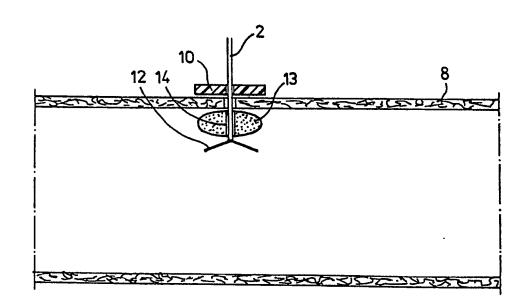












INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 90/00078 I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) * According to International Patent Classification (IPC) or to both National Classification and IPC IPC⁵: A 61 B 17/12 II. FIELDS SEARCHED Minimum Documentation Searched 7 Classification System Classification Symbols IPC⁵ A 61 B Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched * III. DOCUMENTS CONSIDERED TO BE RELEVANT Category * Citation of Document, 11 with Indication, where appropriate, of the relevant passages 12 Relevant to Claim No. 13 Α US, A, 4744364 (KENSEY) 17 May 1988 1,8 see column 3, line 66 - column 4, line 9; column 4, lines 26-30; column 5, lines 28-34; figure 4 (cited in the application) * Special categories of cited documents: 18 later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention. "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filling date "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed "4" document member of the same patent family IV. CERTIFICATION Date of Mailing of this International Search Report Date of the Actual Completion of the International Search 27th September 1990 **1** 5. 10. 90 Signature of Authorized Officer International Searching Authority EUROPEAN PATENT OFFICE H. Ballesteros

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

NL 9000078

SA 37659

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/10/90

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Patent document	Publication	Patent family		Publication date
cited in search report	date	member(s)		
US-A- 4744364	17-05-88	JP-A- US-A- US-A-	63246148 4852568 489u612	13-10-88 01-08-89 02-01-90

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